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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,809	07/03/2001	Raghavan Rajagopalan	MRD/63	5120

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EXAMINER
MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/898,809	RAJAGOPALAN ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *3-10 and 15-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11-14 and 23-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This action is in response to amendments filed on 2/27/03. Applicant has amended claims 1, 2, 12, and 14. There are thirty claims pending and fourteen under consideration. Claims 1, 2, and 11 are composition claims. Claims 12-14 and 23-30 are use claims. This is the first action on the merits. The application concerns some t cyanine dye compositions and uses thereof.

Response to Amendment

2. Applicants' amendments overcome the objections made in points #4-#7. Applicants' amendment, clarifying that they are claiming compositions, not compounds, overcomes the indefiniteness rejection made in point #8 concerning comprising. Applicants amendments, clarifying in the Examiners' eyes what they mean by cyanine dye overcomes the indefiniteness rejections made in point #14 and #15 as well as the written description rejection made in point #18. Applicants' definition concerning the "conjugated azamethine" compounds would be recognized by the skilled dye chemist and finds support in the standard reference work, LaRive (Chemistry of Heterocyclic Compounds). These are terms of art in the photographic chemical arts. Thus, no new matter is introduced by these changes.

Election/Restrictions

3. This application contains claims 3-10 and 15-22 drawn to an invention nonelected with traverse in Paper No. 4. A complete reply to the final rejection

must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Objection is made to claims 1, 11-13, and 23-30 as containing non-elected subject matter. The claimed compounds, compositions, and methods that employ them present a variable core. Formula of claim 1 contains compounds drawn to the non-elected inventions to the extent it contains DYE radicals other than cyanines.

Claim Rejections - 35 USC § 112

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1, 2, 11-14, 23-30 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "somatostatin receptor binding molecule" ... "carbohydrate receptor binding molecule" are all indefinite for two reasons. "E" cannot be a molecule, which lacks any free valence, it must be a univalent radical. Claims 1, 2, 11-14, 23-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "somatostatin receptor binding molecule" ... "carbohydrate receptor binding molecule" are all indefinite for two reasons. "E" cannot be a molecule, which lacks any free valence, it must be a univalent radical.

6. Secondly, what are the chemical structures of these fragments that define radical "E"? These are not art-recognized terms. The passage spanning line 17, page 12 to line 12, page 13 lists the function that these radicals are to perform, but does not clarify the molecular structures. Applicants' statement that "E" is an epitope only further clouds the issue. The Examiner understands that an epitope is a portion of a protein chain in an antibody. Is "E" an antibody or only a short peptide segment from an antibody? Are the synthetic biomolecules listed in lines 11-13, page 13 "E"?

Search of the US Patent full text file for the phrases reveals only five previous uses, in US Patent 6,485,704 B1 and in published applications, US 20030072763 A1, US 20030036538 A1, US 20030017164 A1, US 20020169107 A1, and US 20020164287 A1. All of these are by the present Applicants. While the phrases may be understood in the Applicants' own laboratory, no other scientists would know what radicals are intended.

7. Claims 1, 2, 11-14, 23-30 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specific phrase "carbohydrate receptor-binding molecule" is indefinite. There is an entire class of such carbohydrate receptors, quite possibly thousands, and generally

poorly understood and characterized. How would one know if any molecule E bound to such a receptor without checking all such receptors?

8. What does "associated with biomolecules" mean in claim 11 in Applicants definition of "E". Are Applicants' claiming these substances, or antibodies to these? Must "E" be a peptide segment of an antibody or can it be a hormone, amino acid etc?

These four indefiniteness rejections will be considered together. Applicants refer to a declaration by Dr. Rajagopalan and point to two passages in the specification lines 17-18, page 12 and line 21, page 14 to line 2, page 15 as clarifying the structure of the radicals they claim. This is not persuasive. Firstly, no such deceleration was found in the file. Applicants are remained that any such declaration should contain data in terms of citations to patents, review articles, and scientific papers to show that the meaning of such function terms are art recognized. The declaration should not simply contain allegations by Applicant that such terms are understood by one of skill in the chemical arts. Mere allegations are not probative. *In re CHILOWSKY*, 134 USPQ 515, "[i]n this respect they are not only expressions of opinion but incompetent expressions. We have been unable to find in the facts which the affidavits support a basis for deciding that Chilowsky has complied with the requirements of section 112.", *In re*

LINDELL, 155 USPQ 521. Secondly, the passages to which applicants point define the function of the radicals they claim. The passages contain open language, "for example" and give limited directions for how to even find such radicals. Direction to seek such radicals does not substitute for chemical formulas giving the structures of such radicals.

9. Claim 11 recites the limitation "associated with ... monoclonal antibodies, polyclonal antibodies, receptors [and] receptor binding molecules" in lines 5 and 6. There is no antecedent basis for this limitation in the parent claim 1, which lists seven specific receptors, not all receptors or all molecules that bind to any receptor. This would require testing all antibodies to every antigen to determine what is included by this claim.

Applicants make no specific argument concerning this rejection. The Examiner is considering this separately because claim 11 is simply broader in scope than the parent claim upon which it depends, independently of the meaning of the terms in the parent claim.

10. Claims 1, 2, 11-14, 23-30 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for radical "E" being dihydroxyindolecarboxylic acid or the peptide Cytate, does not reasonably provide enablement for all the other offered E binding molecules. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. If E is an epitope from an antibody, raising all possible antibodies to the somatostatin receptor and locating all the possible epitope sites on these antibodies is an impossible task. Alternatively, screening all "hormones, amino acids, peptides, ... and aptamers" to determine if they bind to the receptors listed in claim 1 is an open-ended and potentially inconclusive research project.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims." *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

Locating the epitope on any particular antibody to a somatostatin receptor say, would a moderate degree of experimentation. However, all possible antibodies would have to be made because the individual epitope sites would differ. The direction concerning the compounds claimed is found in Figure 2. In that figure, the radical "E" is described as "Biomolecule". Thus, Figure 2 does not

appear to be a working example. There are no working examples of a compound of formula given in claim 1. There is no procedure given to determine the affinity of any substance to the receptors listed in claim 1. The state of the art for tumor binding agents is given in the references spanning line 22, page 13 to line 5, page 14. The artisan using Applicants invention would be a medicinal chemist Ph. D. degree in chemistry and several years experience making bioconjugates. The predictability in art of preparing antibodies is low. The absence of working examples and the absence of any of the above references teaching the determination of any epitope implies that predictability is small. Reference AR teaches the use of an octapeptide which binds to the somatostatin receptor. A radical which derived from this peptide would fit the definition of "E" but is unclear if there additional such peptides or how the peptide Cytate was identified. The scope of the claimed subjected matter, as far as the "E" radical, is large.

Applicants argue that the declaration discussed above provides enablement and focusing upon steroids argues that the skilled medicinal chemist understands the structures of steroids. The absence of any declaration was discussed above. The argument concerning steroids is not persuasive for three reasons. Firstly, the claim limitation is "steroid receptor binding molecules". Not all compounds that bind to a steroid receptor are steroids. For example, diethyl stilbesterol (DES) does

not contain the cyclopentylphenanthrene ring system of the steroid, yet DES binds to the estrogen steroid receptor. In fact, a cottage industry has sprung up searching successfully for non-steroidal compounds that bind to the estrogen receptor with *presumably toxic effects*. Secondly, Applicants are reminded of the fact situation of *In re Kirk and Petrow*, 153 USPQ 48, where the U.S. Court of Customs and Patent Appeals held, " it is appropriate to note that the specification does not even intimate that the claimed compounds of the spirostane and pregnane series themselves have "biological activity," much less the specific progestational, glucocorticoid or anti-inflammatory activities mentioned in the affidavit. With respect to the eighteen androstanes that are disclosed, five of which are claimed here, it is said they "are of value * * * in some cases on account of their biological properties." (Emphasis supplied.) There is no suggestion which androstanes are of value for that reason, or what biological properties make them useful." Spirostane, pregnane, and androstanes are all steroids. Applicants are reminded of the legal conclusion reached in *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 by the U.S. Court of Appeals Federal Circuit, "[a] description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its function of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function.". Thirdly, directions to the biochemist

for how to search for molecules meeting Applicants' functional limitations, do not substitute for direction to the organic process chemist of how to make Applicants' claimed radicals.

11. Claims 1, 2, 11-14, 23-30 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The issue concerning the meaning of phrases "somatostatin binding molecule" ... "carbohydrate binding molecule" *etc* are discussed above.

According to the MPEP §2163 I. A. "the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." The MPEP states in §2163 II 3. ii) "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice

(see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406." Applicants have disclosed no species and have made no assertion that there is any correlation between the function of radical "E" and its structure.

Applicants correctly point out that this is issue is factually related to the indefiniteness issue of the meaning of "somatostatin receptor binding molecules" *etc.* The examiner agrees but a asserts a distinct legal issue is involved, namely if Applicants know the structures of the molecules they are attempting to patent. Applicants do assert that the skilled medicinal chemist would understand the structures involved but provide no evidence to that point. The Examiner has presented evidence that the meaning is not widely understood. Applicants are reminded of the legal conclusion reached in *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 by the U.S. Court of Appeals Federal Circuit, " We next address Enzo's additional argument that the written description requirement for the generic claims is necessarily met as a matter of law because the claim language appears in

ipsis verbis in the specification. We do not agree. Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement."

12. Claims 12-14 and 23-30 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific diseases listed in the specification, does not reasonably provide enablement for treating every "target tissue". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification does not set forth any steps involved in determining how to identify "a target tissue". It is unclear what diseases and treatments applicant is intending to encompass. In which diseases do these targets exist? Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out such clinical research to identify the tissues and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

In lines 14-16, page 2, line 18, page 2, and the lines spanning line 22, page 2 to line 2, page 3 Applicants discuss specific diseases amenable to photo therapy. The Examiner suggests claiming treatment of these specific diseases.

13. Applicants argue that they have provided numerous representative examples of such treatment. They also assert that the skilled physician could search for the target tissue and thus determine which diseases to treat. This is not persuasive. Firstly, there are no working examples of any disease treatment in the specification. Secondly, brief description of how to search fro is hardly the same as detailed description of how to use. Thirdly, performing the clinical trials on the millions of compounds embraced by the present claims would require a huge amount of experimentation. Thus, the amount of experimentation required to practice Applicants disease treatment claims would be excessive.

Conclusion

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for after final amendments is (703) 872-9307. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mukund Shah
Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
May 9, 2003